AMENDMENTS TO THE CLAIMS

1. (Currently Amended) A composition comprising:

a) a substrate with a surface comprising discrete wells~~sites;~~, wherein each of said wells is configured to hold a single microsphere;

b) a reflective layer coating the bottom of the wells~~on said surface~~; and

c) a population of microspheres distributed in said wells ~~on said substrate said microspheres comprising at least a first and a second subpopulation~~.

2. (Currently Amended) A composition according to claim 1 wherein at least one of said microspheres ~~subpopulation~~ comprises a bioactive agent.

3. (Currently Amended) A composition according to claim 2, wherein said bioactive agent is fluorescent~~, wherein said substrate comprises a first and a second surface, wherein said first surface comprises said discrete sites, said reflective coating on said second surface, said population of microspheres distributed on said first surface~~.

4. (Currently Amended) A composition according to claim 1 ~~or claim 3~~, wherein said substrate is a fiber optic bundle.

5. (Currently Amended) A composition according to claim 1, wherein said substrate is planar~~4, wherein said fiber optic bundle comprises wells comprising said microspheres~~.

6. (Currently Amended) A composition according to claim 1 ~~or claim 3~~, wherein said substrate is selected from the group consisting of: glass and plastic.

7. (Currently Amended) A composition according to claim 1 ~~or claim 3~~, wherein said reflective layer ~~coating is~~ comprises a metal.

8. (Original) A composition according to claim 7, wherein said metal is selected from the group consisting of gold, silver, chromium, platinum and indium tin oxide.

9. (Currently Amended) A composition according to claim 1, ~~or claim 3~~ wherein said reflective layer~~coating~~ is a dielectric coating.

10. (Currently Amended) A composition according to claim 1 ~~or claim 3~~, wherein said reflective layer~~coating~~ selectively absorbs certain wavelengths of light.

11-16. (Cancelled)

17. (Currently Amended) An array composition comprising:

a substrate with a surface comprising an array of ~~discrete sites comprising alternatively shaped~~ wells, wherein each of said wells is configured to hold a single microsphere;

a reflective layer coating the bottom of the wells; and

a population of microspheres disposed in said wells, wherein said microspheres are linked to a bioactive agent.

18. (Currently Amended) A composition according to claim 17, wherein the wall angle of said ~~alternatively shaped~~ wells is a sloped wall angle.

19. (Currently Amended) A composition according to claim 17, wherein said ~~alternatively shaped~~ wells contain a rounded wall interior.

20. (Original) A composition according to claim 17, wherein at least one of said alternatively shaped wells is a geometrically shaped well.

21. (Currently Amended) A composition according to claim 17 ~~20~~, wherein said wells have ~~geometrically shaped well has~~ a cross section selected from the group consisting of a square, a hexagon, a star, a triangle, a pentagon and an octagon.

22. (Currently Amended) A composition according to claim 17, wherein said bioactive agent is fluorescent~~further comprising a population of microspheres distributed in said wells~~.

23. (Currently Amended) A composition according to claim 17, wherein said bioactive agent comprises DNA~~22, wherein said population comprises at least first and second subpopulations, each of said subpopulations comprising a bioactive agent~~.

24 - 28. (Cancelled)

29. (Currently Amended) An array composition comprising:

a) a substrate with a surface comprising discrete wells, wherein each of said wells is configured to hold a single microsphere,~~sites~~; ~~and~~

b) a reflective layer coating the bottom of the wells; and

c)~~b)~~ a population of microspheres distributed in said wells~~on said substrate~~,

wherein said microspheres comprise:

i) a bioactive agent; and

ii) a signal transducer element.

30. (Original) A composition according to claim 29, wherein said signal transducer element is a nucleotide intercalator.

31. (Original) A composition according to claim 29, wherein said signal transducer element is a fluorophore.

32-47. (Cancelled)

48. (New) The composition of claim 1, wherein said microspheres comprise a first and a second population of microspheres.

REMARKS

Applicants wish to thank the Examiner for withdrawing the 102(e) rejection in view of U.S. Patent No. 6,023,540 to Walt et al. (Walt). Claims 1-10, 17-23, 29-31 and 48 are presented for examination. Claims 11-16 and 24-28 are cancelled and Claims 1-7, 9-10, 17-19, 21-23, and 29 have been amended.

Examples of support for the amendments are as follows: Claims 1, 17, and 24: page 12, lines 1-7, page 9, lines 24-34, page 24, lines 31-32, and Figure 14, Claim 2: page 4, lines 15-18, Claims 3 and 22: page 25, lines 16-19 and Figure 10, Claim 4: page 4, lines 28-32, Claim 5-6: page 10, lines 35-36 and page 11, lines 1-5, Claim 7, page 48, lines 4-7, Claims 9-10: page 12, lines 6-7, Claim 18-19, page 7, lines 10-12, Claim 21, page 14, lines 13-21, and Claim 23, page 19, lines 26-27. Accordingly, no new matter has been added. Reconsideration of the present case is respectfully requested.

Summary of Interview

Applicants wish to thank the Examiner for allowing Applicants to conduct an interview on September 23, 2003 to discuss the pending claims and the scope of the cited art. While no agreement with respect to the claims was reached, potential amendments were discussed to define the invention in view of the art cited in the March 26, 2003 Office Action.

Discussion of Rejection Under 35 U.S.C. § 102

Claim 47 stands rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 6,198,577, to Kedar et al. (Kedar). As Claim 47 is now cancelled, the rejection over Kedar is now moot.

Claims 1-8, 10, and 29-31 stand rejected under 35 U.S.C. § 102(a) as being anticipated by Barker et al., *Analytical Chem.*, 70:4902-06, (1998) (Barker). Applicants respectfully disagree.

To be anticipatory under 35 U.S.C. § 102, a reference must teach each and every element of the claimed invention. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379 (Fed. Cir. 1986). "Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. ...There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention." *See Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565 (Fed. Cir. 1991).

The rejected claims are directed to substrates comprising wells coated with a reflective layer. When a fluorescent microsphere is placed inside the well and an optical signal is applied, the reflective layer intensifies the optical signal of the microsphere, thus allowing for a more efficient signal collection. *See,* Specification, page 11, lines 18-26 and page 12, lines 6-7. Specifically, the optical signal of the microsphere itself is reflected, thereby increasing the signal of the microspheres. *See,* Specification, page 11, lines 19-2, and Figure 14.

In contrast, Barker teaches fiber optic sensors containing fluorescein derivative dye attached to colloidal gold. *See*, Barker Abstract. The fluorescein dye rearranges as nitric oxide absorbs onto the gold, inducing a decrease in the fluorescence intensity of the dye. *See* Barker Abstract and page 4902, col. 2, lines 29-31. Reference dye microspheres are then added to the fiber to make the nitric oxide sensors ratiometric. *Id.* Barker fails to teach the use of wells, wells coated with a reflective layer, or wells configured to hold a single microsphere. Moreover, there is no suggestion in Barker to modify the disclosed fiber optic sensors by adding wells.

As Barker does not teach wells in any form, it fails to teach each and every element of Claims 1-8, 10, and 29-31. Accordingly, this reference cannot anticipate these claims. For this reason, Applicants respectfully request the withdrawal of the rejection of Claims 1-8, 10, and 29-31.

Discussion of Rejection Under 35 U.S.C. § 103

Claims 17-20 and 22-23 stand rejected under 35 U.S.C. § 103(a) over Barker in view of Walt. Claim 9 stands rejected under 35 U.S.C. §103(a) over Barker in view of U.S. Patent No.

5,896,227 to Toriumi et al. (Toriumi). Claim 21 stands rejected under 35 U.S.C. §103(a) over Barker, in view of Walt, and further in view of Kedar. Claim 24 is rejected under 35 U.S.C. §103(a) over Barker, in view of Walt, and further in view of Toriumi. Applicants respectfully disagree.

To establish a *prima facie* case of obviousness a three-prong test must be met. First, there must be some suggestion or motivation, either in the references or in the knowledge generally available among those of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success found in the prior art. Third, the prior art must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

As discussed above, Barker does not teach wells, wells coated with a reflective layer, or wells configured to hold a single microsphere. In addition, the combination of Barker with Walt does not cure this defect. With respect to claims 17-20 and 22-23, the Examiner argued that it would have been obvious to combine the reflective colloidal gold taught by Barker with the teachings of Walt. Applicants strongly disagree.

As discussed above, the colloidal gold disclosed in Barker is not used as a reflective layer coating the bottom of a well. Rather, Barker makes clear that the fluorescence intensity of the fluorescein dye decreases as nitric oxide adsorbs on the gold. *See* Barker, page 4902, col. 2, lines 29-31. Accordingly, if a skilled artisan wanted to make or use a reflective layer, they would not have been motivated to use the colloidal gold disclosed in Barker because the colloidal gold would not provide a reflective layer or intensify the optical signals disclosed in Walt. Indeed, Barker teaches away from the claimed invention, as it demonstrates that a gold colloid is capable of quenching a fluorescent signal.

Even were a *prima facie* showing of obviousness set forth, Applicants submit that sufficient objective evidence of nonobviousness exists to rebut such a showing. The Federal Circuit has held that these secondary considerations should be considered in every case for the probative value they have. *Stratoflex, Inc. v. Aeroquip Corp.*, 218 U.S.P.Q. 871, 879 (Fed. Cir. 1983) ("[a]ll the evidence on the question of obviousness must be considered"); *See also*,

Gambro Lundia AB v. Baxter Healthcare Corp., 110 F.3d 1573, 1579 (Fed. Cir. 1997) (holding that these objective indicia may often be the most probative and cogent evidence of nonobviousness in the record.) Secondary considerations include...unexpected results of the claimed invention. *In re Rouffet,* 149 F.3d 1350, 1355 (Fed. Cir. 1998). Specifically, evidence of nonobvious or unexpected advantageous properties, such as superiority in a property the claimed composition shares with the prior art, can rebut *prima facie* obviousness. *See* MPEP §716.02(a) and *In re Chupp*, 816 F.2d 643, 646 (Fed. Cir. 1987).

Applicants were the first to discover the unexpected advantages of coating a microsphere well with a reflective coating. Specifically, Applicants loaded fluorescein-labeled microspheres into two different etched fiber bundles: one coated with a thin palladium film, the other uncoated. Specification, page 48, lines 8-12. The average intensities of a subset of microspheres and empty cores were measured for each fiber and graphed in Figure 2a. *Id.* The results indicated that a substantial reduction in background of the metal-coated fiber as compared to the uncoated fiber, resulted in a 10-fold improvement of the signal-to-background ratio. *Id.* Accordingly, Applicants achieved a signal, ten times greater than methods common in the art. This level of signal amplification would be unexpected to one of ordinary skill in the art. For the above stated reasons, Applicants respectfully traverse this rejection and respectfully request withdrawal of the obviousness rejections of Claims 17-20 and 22-23.

With respect to Claim 9, the Examiner essentially argued that this claim would have been obvious in view of Barker and Toriumi. Applicants respectfully disagree. Claim 9, which depends from Claim 1, recites a well that is configured to hold a single microsphere. In contrast, neither Toriumi (See Figures 2 and 3) nor Barker (see discussion above) taken alone or in combination disclose these types of wells. Thus, the cited art fails to teach or suggest each and every claim limitation. Accordingly, Applicants respectfully request the withdrawal of this rejection and the allowance of Claim 9.

With respect to the rejection of Claim 21 over Barker, in view of Walt, and further in view of Kedar, Applicants respectfully disagree for the same reasons relating to the rejections of Claims 17-20 and 22-23. As discussed in detail above, the combination of these references still

does not teach a substrate that has wells coated with a reflective coating, and wherein each of the wells is configured to hold a single microsphere. Accordingly, Applicants respectfully traverse, and request allowance of Claim 21.

With respect to Claim 24, this rejection is now moot as this claim has been cancelled.

CONCLUSION

Applicants have endeavored to address all of the Examiner's concerns as expressed in the outstanding Office Action. Accordingly, amendments to the claims, the reasons therefor, and arguments in support of the patentability of the pending claim set are presented above. Any claim amendments which are not specifically discussed in the above remarks are made in order to improve the clarity of claim language, to correct grammatical mistakes or ambiguities, and to otherwise improve the capacity of the claims to particularly and distinctly point out the invention to those of skill in the art. In light of the above amendments and remarks, reconsideration and withdrawal of the outstanding rejections is specifically requested.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410. If the Examiner finds any remaining impediment to the prompt allowance of these claims that could be clarified with a telephone conference, the Examiner is respectfully requested to initiate the same with the undersigned.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: September 25, 2003

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